

REMARKS

I. Status of the Claims

Claims 1-31 were filed with the application. Claims 2, 3, 5-8 and 10-31 have been withdrawn from consideration. Thus, claims 1, 4 and 9 are under consideration and stand rejected under 35 U.S.C. §112, first paragraph (enablement). The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

Claim 1 is objected to as broader than the elected invention. Applicants will address that objection at the time that all rejections have been overcome.

II. Rejection Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 1, 4 and 9 remain rejected for alleged lack of enablement. As explained below, applicants again traverse.

As stated before, the rejection seems to have two aspects. First, there is a question regarding the ability to extrapolate from the acknowledged role of MEF2C in hypertrophic signaling to other MEF2 isoforms, *i.e.*, MEF2A, MEF2B and MEF2D. Second, the examiner argues that even given the proven role of MEF2C in hypertrophy, the specification provides insufficient evidence regarding efficacy. Applicants believe that the extrapolation from MEF2C to other isoforms is indeed warranted. Moreover, applicants submit that simply alleging unpredictability cannot shift the burden to applicants to provide clinical evidence of efficacy.

Addressing the latter issue first, the examiner argues that to the extent applicants rely on the prior art for enablement of, *e.g.*, gene therapy, applicants are also handicapped by the shortcomings of that art. However, just because there are limitations with respect to, *e.g.*, gene therapy, that does not mean that one of skill in the art cannot make and use the invention. Thus,

the field of gene therapy is to the point where general allegations regarding targeting, duration of expression and specificity simply do not stand up. The PTO has issued hundreds of patents on such therapies, and regardless of the fact that “each application is examined on its own merits,” the PTO cannot now maintain that gene therapy is *per se* not enabled. There are simply too many examples where the alleged limitations to gene therapy have been overcome, circumvented or otherwise are not relevant. Thus, an attack on *this* form of gene therapy should have *some* bearing of limitations that are *unique* to this invention. In other words, it is entirely inappropriate to cast *generalized* dispersions on the claimed invention, but then turn around and require *specific* evidence of efficacy. Simply put, the PTO cannot “have its cake and eat it too.”

The only specific attack on MEF2 gene therapy is that inhibiting MEF2 generally would not be believed to inhibit cardiac hypertrophy. With all due respect to the PTO, applicants have submitted an expert declaration and a recently published paper on this precise point, both documents *supporting* the position that down-regulating MEF2 would indeed be therapeutic of cardiac hypertrophy. The examiner attempts to argue that Xu *et al.* proves this not to be the case by selectively quoting from the article. However, the concluding statement from that paper, which is far more indicative of the authors’ conclusions than the examiner’s quotations, *supports* applicants’ position: “In conclusion, we provide the first proof-of-principle that MEF2 can dominantly drive dilated cardiomyopathy *in vivo*, potentially in association with a primary alteration in a subset of ion handling genes and extracellular matrix associated genes.” This statement *clearly* supports MEF2 as a target, and taken with applicants’ declaratory evidence, it is submitted that the record supports, and does not refute, enablement.

Though not required, applicants provide yet further evidence of the equivalence of various MEF2 isoforms. In the attached declaration of Dr. Tim McKinsey, two panels describe

experiments with one month-old MEF2D knockout mice. Fig. A shows both the knockouts and wild-type littermates subjected to sham operation or thoracic aortic banding (TAB) for 20 days. TAB induced a 27% increase in heart weight-to-tibia length ratio, indicative of cardiac hypertrophy. The hypertrophic response to TAB was eliminated in animals lacking a functional *MEF2D* gene. Fig. B shows animals were treated as described in Fig. A. Left ventricles were fixed and stained with hematoxylin (red) and Mason's trichrome (blue) to reveal cardiac muscle and fibrotic lesions, respectively. Thus, this figure shows the MEF2D, in addition to MEF2A and MEF2C, plays a role in cardiac hypertrophy.

Another efficacy-related point raised by the examiner, also raised in prior actions, is the question of *how* one would seek to inhibit MEF2. It is again argued that no materials necessary to practice the claimed invention are provided. Again, as noted in the previous response, this is not true. Pages 23-30 provide a detailed explanation of *how* one can achieve inhibition of MEF2 signaling:

Thus, in a particular embodiment of the present invention, there are provided methods for the treatment of cardiac hypertrophy. These methods exploit the inventors' observation, described in detail below, that MEF2 appears to up-regulate the expression of genes involved in the hypertrophic response. At its most basic, this embodiment will function by reducing the *in vivo* activity of MEF2 in individuals suspected of having undergone a hypertrophic response, currently undergoing a hypertrophic response, or in danger of cardiac hypertrophy. This may be accomplished by one of several different mechanisms. First, one may block the expression of the MEF2 protein. Second, one may directly block the function of the MEF2 protein by providing an agent that binds to or inactivates the MEF2 protein. And third, one may indirectly block the effect of MEF2 by interfering with one or more targets of MEF2.

Specification at page 23. The text goes on to describe a variety of materials that can be used to implement each of these embodiments, and how they can be administered. For example, page 24 of the specification states that "[t]he therapeutic compositions of the present invention may be

administered in a manner similar to the administration of current treatments for heart conditions, such as aspirin, nitrates and beta blockers.” Agents such as antisense polynucleotides, ribozymes, organochemical compositions, antibodies that block an active site or binding site on MEF2, or molecules that mimic an MEF2 target are all described. Thus, it is untrue that the specification fails to provide such information, and applicants are at a loss to explain further since the examiner failed to comment on their previous submission in the latest action.


Finally, returning to the first issue which is only briefly alluded to in the most recent action, applicants again submit that the demonstrated equivalence between MEF2A and MEF2C (and now MEF2D) provides sufficient basis for claiming isoforms of MEF2 generally, and the examiner has not provided a specific rebuttal of this position.

In sum, upon review of the relevant *Wands* factors, the evidence submitted *in favor* of applicants’ position and the dearth of *evidence* supporting the PTO’s position, it is again submitted that the PTO has failed to shift the burden to applicants to defend their presumptively enabling disclosure. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Reconsideration and withdrawal of the rejection is respectfully requested.

III. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should Examiner Woitach have any questions regarding this response, she is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



Steven L. Highlander
Reg. No. 37,642
Attorney for Applicant

FULBRIGHT & JAWORSKI
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3184

Date: September 12, 2006